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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/042,460	03/16/1998	GREGG B. MORIN	015389003110	5004

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EXAMINER
KAUSHAL, SUMESH

ART UNIT	PAPER NUMBER
1636	

DATE MAILED: 02/13/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/042,460	MORIN ET AL.	
	Examiner	Art Unit	
	Sumesh Kaushal Ph.D.	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *27 November 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *5,9,20-28 and 31-34* is/are pending in the application.

4a) Of the above claim(s) *5 and 9* is/are withdrawn from consideration.

5)☐ Claim(s) *21,22,24,25 and 27* is/are allowed.

6)☒ Claim(s) *20,23,26,28 and 31-34* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 11/27/02 has been entered.

Claims 20-28 and 31-34 were examined in this office action..

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn. The references cited herein are of record in a prior Office action.

► *If the claims are amended, added and/or canceled in response to this office action the applicants are required to follow Amendment Practice under 37 CFR § 1.121 (http://www.uspto.gov) and A CLEAN COPY OF **ALL** PENDING CLAIMS IS REQUESTED.*

Applicant's arguments filed 11/27/02 have been fully considered but they are not persuasive, for the reasons of record as set forth in the earlier office action (Paper No.31, 02/28/02).

Oath/Declaration

The oath or declaration is defective. A new oath or declaration in compliance with 37 CFR 1.67(a) identifying this application by an application number and filing date is required. See MPEP §§ 602.01 and 602.02.

The oath or declaration is defective because: After applicant's amendment on 02/14/00 the instant application claims priority only to US App. No. 08/979, 742 filed 11/26/97, and **not to the other US or PCT applications** as stated in the declaration. Appropriate correction is required.

The applicant fails to correct this defect in the response filed on 11/27/02

Claim Objections

Claims 32-34 are objected to because of the following informalities: The instant claims recites limitation "shown in figure 5" and fails to recite the required SEQ ID NO.

> 37 CFR 1.821(d) requires the use of the assigned sequence identifier in all instances where the description or claims of a patent application discuss sequences regardless of whether a given sequence is also embedded in the text of the description or claims of an application.(see MPEP 2422.03)
>
> Appropriate correction is required.

The applicant fails to correct this defect in the response filed on 11/27/02

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

Claim 31 is rejected under 35 U.S.C. 102(a) as being clearly anticipated by Nakamura et al (Science 277:955-959, 1997, see attached PTO sequence search report). The cited art teaches a polynucleotides sequence encodes a protein containing at least 10 consecutive amino acid sequence of SEQ ID NO:2. Thus the invention as claimed has been clearly anticipated by the cited prior art of record.

Claim 28 is rejected under 35 U.S.C. 102(a) as being clearly anticipated by Greider et al (WO97/35967, 1997). The cited art teaches generation of mouse WW6 ES cells wherein the endogenous mTR (mouse telomerase) gene has been knocked out via homologous recombination (page 24-25). The cited art further teaches generation of mice homozygous null for mTR gene

(page 27, example-6; page 28, table-1). In addition the cited art teaches generation of conditional mTR deletion in specific tissues (page 30, example-7). Thus the cited art clearly anticipated the invention as claimed.

Claim Rejections - 35 USC § 112

Claims 20, 23, 26 and 31-34 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for an isolated polynucleotide encoding mouse mTERT protein wherein the protein has at least 90% sequence identity to SEQ ID NO:2, and the protein contains mouse Motif- T, Motif-1, Motiff-2, Motiff-A, Motiff-B, Motiff-C and Motiff-D and has telomerase catalytic activity when associated with telomerase RNA component, does not reasonably provide enablement for any natural and/or non-natural TERT proteins that have at least 90% sequence identity to SEQ ID NO:2 and has telomerase catalytic activity when associated with a telomerase RNA. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention **commensurate in scope** with these claims, for the same reasons of record as set forth in the official action mailed on 02/28/02.

Nature Of Invention:

The instant invention is drawn to an isolated polynucleotides sequence encoding a telomerase reverse transcriptase protein wherein the protein has at least 90% identity to the amino acid sequences of SEQ ID NO:2.

Breadth Of Claims And Guidance Provided By The Inventor:

The scope of instant claims encompass an isolated nucleic acid molecule encoding a telomerase reverse transcriptase protein and its natural or non-natural variants, which has at least 90% sequence identity to amino acid sequences of SEQ ID NO:2. At best the specification only discloses the nucleic acid encoding SEQ ID NO:2 having telomerase catalytic activity when associated with telomerase RNA component (mouse mTERT) but fails to disclose a single variants of SEQ ID No:2 that have any mTERT like activity.

State Of Art And Predictability:

The state of the art concerning telomerase teaches that telomerase-complex consists of TERT protein, RNA component and other TRT associated proteins. Furthermore, TERT protein consists of several conserved motifs that are required for the telomerase activity (Lundblad, PNAS 95:8415-8416, 1998, *ref of record*). Furthermore, it is general knowledge in the art that even conservative amino acid substitutions can adversely affect proper folding and biological activity if amino acids that are critical for such functions are substituted, and the relationship between the sequence of a polypeptide and its tertiary structure is neither well understood nor predictable. In addition, mere identification of critical regions would not be sufficient, as the ordinary artisan would immediately recognize that the encoded polypeptide must assume the proper three-dimensional configuration to be active, which is dependent upon the surrounding residues. (see Ngo, in The Protein Folding Problem and Tertiary Structure Prediction, Merz et al. (eds.), Birkhauser Boston: Boston, MA, pp. 433 and 492-495, 1994. Rudinger in Peptide Hormones, Parsons (ed.), University Park Press: Baltimore, MD, pp. 1-7, 1976).

Quantity Of Experimentation Required:

The applicant argues that the amino acid variants of SEQ ID NO:2 that has telomerase activity can be obtained without undue experimentation. The applicant argues that office has issued patents with claims reciting degree of identity to a representative species (response, page 4). The applicant further argues that the specification and general knowledge in the art provide considerable guidance as to where alteration may be made (response, page 5 para.1-2). The applicant argues that specification describes number of assays for determining telomerase activity (response, page 5, para.3.). The applicant argues that the mouse and human TRT are only 70% identical yet both demonstrate telomerase activity. The applicant argues that even conserved motifs in DNA-polymerase enzyme are not required for functional activity (response, page 7). The applicant further argues that office has issued over 1000 patents with subject matter defined by degree of relatedness to a representative species (response, page 10). The applicant concluded that the instant specification is relatively rich in describing features of the structure compared to other patents and patent applications for novel proteins and gene sequences. Therefore the applicant is entitled to patent coverage for sequences that are 90% identical to the representative species.

However, this is not found persuasive because the scope of instant claims encompass an isolated nucleic acid molecule encoding a telomerase reverse transcriptase protein and its natural or non-natural variants, which has at least 90% sequence identity to amino acid sequences of SEQ ID NO:2. The instant specification as filed fails to disclose a single polynucleotide sequences that has 90% sequence identity to SEQ ID NO: 2 and has telomerase like activity. Given the broadest reasonable interpretation the invention as claimed encompass a polynucleotide, which encodes a telomerase reverse transcriptase wherein 10% of amino acid sequences are added, deleted or substituted over the entire length of the polypeptide. The variation as claimed also encompasses the conserved motifs that are germane to the telomerase reverse transcriptase activity. Even though applicant argues that the specification provides considerable guidance as to where alteration may be made, limitations appearing in the specification but not recited in the claim are not read into the claim. In re Prater, 415 F.2d 1393, 1404-05, 162 USPQ 541, 550-551 (CCPA 1969). See also In re Zletz, 893 F.2d 319, 321-22, 13 USPQ2d 1320, 1322 (Fed. Cir. 1989). Furthermore, claims are interpreted in light of the specification does not mean that everything in the specification must be read into the claims. Raytheon Co. v. Roper Corp., 724 F.2d 951, 957, 220 USPQ 592, 597 (Fed. Cir. 1983), cert. denied, 469 U.S. 835 (1984). See also MPEP § 2111 - § 2111.01.

Furthermore, the state of the art clearly teaches that telomerase-complex consists of TERT protein, RNA component and other TRT associated proteins. Furthermore, TERT protein consists of several conserved motifs that are required for the telomerase activity (Lundblad, PNAS 95:8415-8416, 1998, *ref of record*). The specification fails to identify the functional attributes of any individual variant(s) other than SEQ ID NO: 2. It is general knowledge in the art that even conservative amino acid substitutions can adversely affect proper folding and biological activity if amino acids that are critical for such functions are substituted, and the relationship between the sequence of a polypeptide and its tertiary structure is neither well understood nor predictable. The variants as claimed are simply hypothetical proteins because no biological function has been established. The mere identification of critical regions would not be sufficient, as the ordinary artisan would immediately recognize that the encoded polypeptide must assume the proper three-dimensional configuration to be active, which is dependent upon the surrounding residues (see Ngo, in The Protein Folding Problem and Tertiary Structure

Prediction, Merz et al. (eds.), Birkhauser Boston: Boston, MA, pp. 433 and 492-495, 1994. Rudinger in Peptide Hormones, Parsons (ed.), University Park Press: Baltimore, MD, pp. 1-7, 1976).

Even though several patents claiming degree of sequence variation has been allowed, applicant's argument alone cannot take place of evidence lacking in the record. Each patent application is examined on its own merit and is considered enabled in view of its own disclosure. The issue is not whether the other application support their claims but whether this application supports its claims "[i]t is immaterial whether similar claims have been allowed to other" In re Gialito 188USPQ 645,648 (CCPA 1976).

The scope of the claims must bear a reasonable correlation with the scope of enablement (In re Fisher, 166 USPQ 19 24 (CCPA 1970)). The courts have clearly stated that: "A specification did not disclose what is well known in the art. See, e.g., Hybritech Inc. V. Monoclonal Antibodies, Inc., 802 F. 2d 1367, 1385, 231 USPQ 81, 94(Fed. Cir. 1986). The general off-repeated statement is merely a rule of supplementation, not a substitute for a basic enabling disclosure. It means that the omission of minor details does not cause a specification to fail to meet the enablement requirement. However, when there is no disclosure of any specific material or of any of the conditions under which a process can be carried out, undue experimentation is required: there is a failure to meet the enablement requirement that cannot be rectified by asserting that all the disclosure related to the process is within the skill of the art. *It is the specification, not the knowledge of one skilled in the art, that must supply the novel aspects of an invention in order to constitute adequate enablement".* Genentech Inc. V. Novo Nordisk A/s, 42 USPQ2d 1005 (CAFC 1997).

In instant case screening of any and all natural and non-natural telomerasere reverse transcriptase variants, wherein at least 10% amino acid are added substituted and/or deleted in the disclosed SEQ ID NO:2 is not considered routine. The applicant fails to point out where in the specification there is support for extensive making and testing of any and all natural and non-natural variants of telomerase as claimed. Making and testing a point mutation is significantly different from the making and testing an amino acid sequences wherein at least 10% amino acids are added, deleted and/or substituted. The number of possible scenarios increase geometrically with increase in percent non-identity. Such making and testing is nothing more than an invitation

to further experimentation, since the specification can not be relied on to teach how to make the variants as claimed. One has to engage in extensive making and testing in order to obtain variants that meet the requirements for the claimed telomerase activity. This is not considered routine in the art and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988). It is noted that the unpredictability of a particular area may alone provide reasonable doubt as to the accuracy of the broad statement made in support of enablement of claims. See Ex parte Singh, 17 USPQ2d 1714 (BPAI 1991). Therefore, one skill in the art would have to engage in excessive and undue amount of experimentation to exercise the invention as claimed, since the applicant has not presented enablement commensurate in scope with the claims.

Claim 28 stands rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, **to make and/or use** the invention, for the same reasons of record as set forth in the official action mailed on 02/28/02.

Nature Of Invention:

Given the broadest reasonable interpretation the invention as claimed falls in the realm of gene therapy and transgenic art. See MPEP § 2111 - § 2111.01.

Breadth Of Claims And Guidance Provided By The Inventor:

The scope of invention as claimed encompasses a mouse cell in vivo, wherein the mouse is transgenic mouse or cell has been manipulated by a method related to a gene therapy technique. At best example-4 teaches the electroporation of pmTERTKO vector in to WW6 ES cells but falls short of disclosing a single cell clone wherein the mTERT gene has been mutated (see example-4, page 114, line 27-31). Similarly, the specification discloses the injection of WW6 ES clones into C57BL/6 blastocytes, wherein the mTERT gene has been knocked out but fails to disclose a single founder animal exhibiting the required phenotype.

State Of Art And Predictability:

Gene therapy is considered highly experimental area of research at this time, and both researchers and the public agree that demonstrable progress to date has fallen short of initial

expectations In addition the delivery of a gene of interest to any cell in vivo using any and all viral and or non-viral vector has been considered highly unpredictable. (Rosenberg et al, Science 287:1751, 2000, Friedmann, Science 287(5461):2163-5, 2000, Anderson WF, Nature 392:25-30, 1998; Verma et al Nature 389:239-242, 1997, *ref. or record*).

The state of transgenic art at the time of filing was such that phenotype of an animal is determined by a complex interaction of genetics and environment. The phenotype examined in a transgenic and knock out model is influenced by genetic background, which is the collection of all genes present in an organism that influence a trait or traits. (see Wood. Comp. Med. 50(1): 12-15, 2000, Sigmund, Arterioscler. Throm. Vasc. Biol.20:1425-1429, 2000, Kappel et al. Current Opinion in Biotechnology 3:558-553 1992, Rossant et al , Phil. Trans. R. Soc Lond. B. 339:137-254, 1993, Viville, in Transgenic Animals, Houdebine (eds), Harwood academic publishers, France. pp307-321, 1997).

Quantity Of Experimentation Required:

The applicant argues that declaration by Choy-Pik Chiu filed with last response provided evidence that knockout animals have been made in the manner described in the specification (response, page15).

However, this is found unpersuasive because the scope of instant claim encompasses a cell that has been transformed in vivo, therefore the invention as claimed not only falls in the realm of transgenic art but also relates to gene therapy. The stat of art clearly teaches that the i) delivery of a gene of interest to any cell in vivo using any and all viral and or non-viral vectors and ii) making a transgenic animal has been considered highly unpredictable. The specification fails to disclose the delivery of polynucleotides as claimed in-vivo using viral or non-viral vectors via any and all routes of administration. In addition claim 28 encompass not only an isolated mouse cell but also include a mouse cell derived from a transgenic mouse (*which is non-elected subject matter, see office action 07/05/00, page 2*) wherein the endogenous mTERT gene has been mutated. The applicant even fails to disclose a single transfected cell wherein any and all components of telomerase complex have been knocked out by recombinant means and an exogenous mTERT gene have been transfected. At best example-4 teaches the electroporation of pmTERTKO vector in to WW6 ES cells but falls short of disclosing a single cell clone wherein the mTERT gene has been mutated (see example-4, page 114, line 27-31). Similarly, the

specification discloses the injection of WW6 ES clones into C57BL/6 blastocytes, wherein the mTERT gene has been knocked out but fails to disclose a single founder animal exhibiting the required phenotype. In addition, Dr. Choy-Pik Chiu's declaration relies on publications that were published after the filing date of instant application, which does not enable instant specification for full scope of invention as claimed.

A genetically engineered cell (in-vivo) wherein an endogenous mTERT gene has been muted by any recombinant means (by method of gene therapy or by any transgenic knock-out technique) has been not considered routine in the art and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988). It is noted that the unpredictability of a particular area may alone provide reasonable doubt as to the accuracy of the broad statement made in support of enablement of claims. See Ex parte Singh, 17 USPQ2d 1714 (BPAI 1991). Therefore, one skill in the art would have to engage in excessive and undue amount of experimentation to exercise the invention as claimed.

Conclusion

Claims 20, 23, 26, 28 and 31-34 are rejected.

Claims 21-22, 24-25 and 27 are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sumesh Kaushal Ph.D. whose telephone number is 703-305-6838. The examiner can normally be reached on Mon-Fri. from 9AM-5PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Yucel Irem Ph.D. can be reached on 703-305-1998. The fax phone numbers for the organization where this application or proceeding is assigned are 703-308-4242 for regular communications and 703-308-8724 for After Final communications. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

S. Kaushal
PATENT EXAMINER

JEFFREY FREDMAN
PRIMARY EXAMINER